

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Hung-Teh Kao, Paul R. Hartig, and Theresa Branchek
Serial No.: Not Yet Known
Filed: Herewith
For: DNA ENCODING A HUMAN SEROTONIN (5-HT₂) RECEPTOR
AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
August 14, 2001

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT

Please amend the subject application as follows:

In the Specification:

On page 1, line 4, please insert the following paragraph:

-- This application is a continuation of U.S. Serial No. 09/145,864, filed September 2, 1998, now allowed, a divisional of U.S. Serial No. 08/613,044, filed March 8, 1996, now U.S. Patent No. 5,885,785, issued March 23, 1999, a divisional of U.S. Serial No. 08/347,591, filed November 30, 1994, now U.S. Patent No. 5,661,024, issued August 26, 1997, a continuation of Serial No. 08/232,325, filed April 25, 1994, now abandoned, a continuation of Serial No. 07/999,661, filed December 29, 1992, now abandoned, a continuation of 07/635,402, filed December 31, 1990, now abandoned, a continuation of Serial No. 07/429,832, filed October 31, 1989, now abandoned, the contents of which are

09/145,864

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 2

hereby incorporated by reference into the subject application.--

In the Claims:

Please cancel claims 4-43, 46, and 49-51 without prejudice to applicants' right to pursue the subject matter of these claims in a future continuation or divisional application.

REMARKS

Claims 1 to 51 were pending in the subject application. By this Amendment, applicants have canceled claims 4-43, 46, and 49-51 without prejudice or disclaimer. Accordingly, upon entry of this Amendment, claims 1, 2, 3, 44, 45, 47 and 48 will be pending and under examination.

Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**EXHIBIT 1**). The following references were previously cited in connection with the prosecution of U.S. Serial Number 09/145,864 from which the subject application claims benefit under 35 U.S.C. §120. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information Disclosure Statement. Accordingly, copies of the following references are not attached to this Information Disclosure Statement:

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 3

1. U.S. Patent No. 4,985,352, issued January 15, 1991, Julius, et al;
2. U.S. Patent No. 5,155,218, issued October 13, 1992, Weinshank, et al.;
3. U.S. Patent No. 5,360,735, issued November 1, 1994, Weinshank, et al.;
4. U.S. Patent No. 5,472,866, issued December 5, 1995, Gerald, et al.;
5. U.S. Patent No. 5,476,782, issued December 19, 1995, Weinshank, et al.;
6. U.S. Patent No. 5,661,024, issued August 26, 1997, Kao et al.;
7. U.S. Patent No. 5,885,785; issued March 23, 1999, Kao et al.;
8. European Patent Application EP 0 565 370, published October 13, 1993;
9. French Patent Application No. 2696749, published April 15, 1994;
10. PCT International Patent Publication No. 95/06117, published March 2, 1995;
11. Kramer, R.A., et al., "Regulated Expression of a Human Interferon Gene in Yeast, Control by Phosphate Concentration or Temperature," *PNAS* 81: 367-370 (1984);
12. Cory, R.N., et al., "5-HT₂ Receptor-Stimulated Inositol

104T89"ET6660

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 4

Phosphate Formation in Rat Aortic Myocyte," *Euro. J. Pharm.*
131: 153-157 (1986);

13. Hoyer, D., et al, "Serotonin Receptors in the Human Brain. II. Characterization and Autoradiographic Localization of 5-HT_{1C} and 5-HT₂ Recognition Sites," *Brain Research* 376: 97-107 (1986);
14. Lyon, R.A., et al, "³H-DOB (4-Bromo-2, 5-Dimethoxyphenylisopropylamine) Labels Guanyl Nucleotide-Sensitive State of Cortical 5-HT₂ Receptors," *Mol. Pharm.* 31: 194-199 (1986);
15. Cory, R.N., et al, "The 5-Hydroxytryptamine (5-HT₂) Receptor Stimulates Inositol Phosphate Formation in Intact and Broken WRK1 Cells: Determination of Occupancy-Response Relationships for 5-HT Agonists," *J.Pharm. Exp. Ther.* 241(1): 258-267 (1987);
16. Shenker, A., et al., "Pharmacological Characterization of Two 5-Hydroxytryptamine Receptors Coupled to Adenylate Cyclase in Guinea Pig Hippocampal Membranes," *Mol. Pharm.* 31(4): 357-367 (1987);
17. Lubbert, H., et al., "cDNA Cloning of a Serotonin 5-HT_{1C} Receptor by Electrophysiological Assays of mRNA-Injected *Xenopus* Oocyte," *PNAS* 84: 4332-4336 (1987);
18. Kobilka, B.K., et al., "An Intronless Gene Encoding a Potential Member of the Family of Receptors Coupled To Guanine Nucleotide Regulatory Proteins," *Nature* 329: 75-79 (1987);

104180"EE62660

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 5

19. Marzoni, G., et al., "6-Methylergoline-8-Carboxylic Acid Esters as Serotonin Antagonists: N¹-Substituent Effects of 5HT₂ Receptor Affinity," *J. Med. Chem.* **30**(10): 1823-1826 (1987);
20. Kaufman, R.J., et al., "High Level Production of Proteins in Mammalian Cells," *Genetic Engineering* **9**: 155-198 (1987);
21. Stevens, et al., "Channel Families in the Brain," *Nature* **328**: 198-199 (1987);
22. Fargin, A., et al., "The Genomic Clone G-21 Which Resembles a β -Adrenergic Receptor Sequence Encodes the 5-HT_{1A} Receptor," *Nature* **335**: 358-360 (1988);
23. Harris, T.J., et al., "Expression Of Eukaryotic Genes in E.Coli," *Genetic Engineering* (1988) **4**: 127-141;
24. Julius, D., et al., "Molecular Characterization of a Functional cDNA Encoding the Serotonin 1c Receptor," *Science* **241**: 558-564 (1988);
25. Pritchett, D.B., et al., "Structure and Functional Expression of Cloned Rat Serotonin 5HT-2 Receptor," *EMBO J.* **7**: 4135-4140 (1988);
26. Pierce, P., et al., "Evidence for Distinct 5-Hydroxytryptamine₂ Binding Site Subtypes in Cortical Membrane Preparations," *J. Neurochem.* **52**: 656-658 (1989);
27. Amstien, R., et al., "Platelet Deactivation by 5HT₂-Receptor Blockade Parallels the antihypertensive Response to Ketanserin," *J. Hypertense.* **7**(4): 255-260 (1989);

REF ID: A66266

Year	Total		Male		Female	
	Number	Rate	Number	Rate	Number	Rate
1970	1,174	1.1	700	1.1	474	1.0
1971	1,246	1.2	740	1.2	506	1.1
1972	1,318	1.3	780	1.3	538	1.2
1973	1,390	1.4	820	1.4	570	1.3
1974	1,462	1.5	860	1.5	602	1.4
1975	1,534	1.6	900	1.6	634	1.5
1976	1,606	1.7	940	1.7	666	1.6
1977	1,678	1.8	980	1.8	698	1.7
1978	1,750	1.9	1,020	1.9	730	1.8
1979	1,822	2.0	1,060	2.0	762	1.9
1980	1,894	2.1	1,100	2.1	794	2.0
1981	1,966	2.2	1,140	2.2	826	2.1
1982	2,038	2.3	1,180	2.3	858	2.2
1983	2,110	2.4	1,220	2.4	890	2.3
1984	2,182	2.5	1,260	2.5	922	2.4
1985	2,254	2.6	1,300	2.6	954	2.5
1986	2,326	2.7	1,340	2.7	986	2.6
1987	2,398	2.8	1,380	2.8	1,018	2.7
1988	2,470	2.9	1,420	2.9	1,050	2.8
1989	2,542	3.0	1,460	3.0	1,082	2.9
1990	2,614	3.1	1,500	3.1	1,114	3.0
1991	2,686	3.2	1,540	3.2	1,146	3.1
1992	2,758	3.3	1,580	3.3	1,178	3.2
1993	2,830	3.4	1,620	3.4	1,210	3.3
1994	2,902	3.5	1,660	3.5	1,242	3.4
1995	2,974	3.6	1,700	3.6	1,274	3.5
1996	3,046	3.7	1,740	3.7	1,306	3.6
1997	3,118	3.8	1,780	3.8	1,338	3.7
1998	3,190	3.9	1,820	3.9	1,370	3.8
1999	3,262	4.0	1,860	4.0	1,402	3.9
2000	3,334	4.1	1,900	4.1	1,434	4.0
2001	3,406	4.2	1,940	4.2	1,466	4.1
2002	3,478	4.3	1,980	4.3	1,498	4.2
2003	3,550	4.4	2,020	4.4	1,530	4.3
2004	3,622	4.5	2,060	4.5	1,562	4.4
2005	3,694	4.6	2,100	4.6	1,594	4.5
2006	3,766	4.7	2,140	4.7	1,626	4.6
2007	3,838	4.8	2,180	4.8	1,658	4.7
2008	3,910	4.9	2,220	4.9	1,690	4.8
2009	3,982	5.0	2,260	5.0	1,722	4.9
2010	4,054	5.1	2,300	5.1	1,754	5.0
2011	4,126	5.2	2,340	5.2	1,786	5.1
2012	4,198	5.3	2,380	5.3	1,818	5.2
2013	4,270	5.4	2,420	5.4	1,850	5.3
2014	4,342	5.5	2,460	5.5	1,882	5.4
2015	4,414	5.6	2,500	5.6	1,914	5.5
2016	4,486	5.7	2,540	5.7	1,946	5.6
2017	4,558	5.8	2,580	5.8	1,978	5.7
2018	4,630	5.9	2,620	5.9	2,010	5.8
2019	4,702	6.0	2,660	6.0	2,042	5.9
2020	4,774	6.1	2,700	6.1	2,074	6.0

28. Wright, D.E., et al, "5-Carboxamidotryptamine Elicits 5-HT₂ and 5-HT₃ Receptor-Mediated Cardiovascular Responses in the Conscious Rabbit: Evidence for 5-HT Release from Platelets," *Cardiovasc. Pharm.* **13(4)**: 557-564 (1989);
29. Strader, C.D., et al, "Structural Basis of β -Adrenergic Receptor Function, *FASEB J.* **3**: 1825-1832 (1989);
30. Schmidt, A.W., et al, "5-Hydroxytryptamine Receptor Families," *FASEB J.* **3**: 2242-2250 (1989);
31. Cohen, M.L., et al., "Lack of a Difference Between Ketanserin and Ritanserin In Central v. Peripheral Serotonin Receptor Antagonism," *Life Sci.* **45(13)**: 1185-1189 (1989);
32. Cohen M.L., et al., "Effect of LY53857, A Selective 5HT₂ Receptor Antagonist on 5HT-Induced Increases in Cutaneous Vascular Permeability in Rats," *Life Sci.* **44(14)**: 957-961 (1989);
33. Baez, M., et al., "Pharmacological and Molecular Evidence that the Contractile Response to Serotonin in Rat Stomach Fundus is Not Mediated by Activation of the 5-Hydroxytryptamine_{1C} Receptor," *Mol. Pharm.* **38(1)**: 31-37 (1990);
34. Branchek, T., et al., "[³H]-DOB(4-Bromo-2, 5-Dimethoxyphenylisopropylamine) and [³H] Ketanserin Label Two Affinity State of the Cloned Human 5-Hydroxytryptamine₂ Receptor," *Mol. Pharm.* **38**: 604-609 (1990);
35. Hartig, P., et al., "The Molecular Biology of Serotonin

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 7

Receptors," *Neuropsychopharmacology* **3(5/6)**: 335-347 (1990);

36. Julius, D., et al., "Distinct by Functionally Conserved Serotonin Receptors," *PNAS* **87**: 928-932 (1990);
37. Saltzman, A.G., et al, "Cloning of the Human Serotoini 5-HT2 and 5HT1C Receptor Subtypes," *Biochem. Biophys. Res. Comm.* **181(3)**: 1469-1478 (1991);
38. Kao, H.T., et al, "Site-Directed Mutagenesis of a Single Residue Changes the Binding Properties of the Serotonin 5-HT2 Receptor from a Human to a Rate Pharmacology," *FEBS Letters* **307(3)**: 324-328 (1992);
39. Mita et al., "Evidence for the presence of D2 and 5-HT2 receptors in the human prefrontal cortex," *Jap. J. Pharmacol.* **32**: 1027-1032 (1982);
40. Bowie, J.U., et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* **247**: 1306-1310 (1990);
41. Wells, J.A., "Additivity of Mutational Effects in Proteins," *Biochemistry* **29(37)**: 8509-8517 (1990); and
42. Ngo, J.T., et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," In: *The Protein Folding Problem and Tertiary Structure Prediction*, pp 492-495 (1994) Merz, K. Jr. and LeGrand, S. (Eds), Birkhauser (Boston).

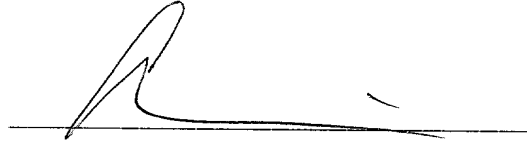
10433 "E.E.660

Hung-Teh Kao, et al.
Serial No.: Not Yet Known
Filed: Herewith
Page 8

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed \$710.00 fee for filing the subject application, is deemed necessary in connection with the filing of this Preliminary Amendment and Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



Alan J. Morrison
Registration No. 37,399
Attorney for Applicants
Cooper & Dunham LLP
1185 Ave of the Americas
New York, New York 10036
(212) 278-0400

RECEIVED